Sepsis and the NIH Clinical Center

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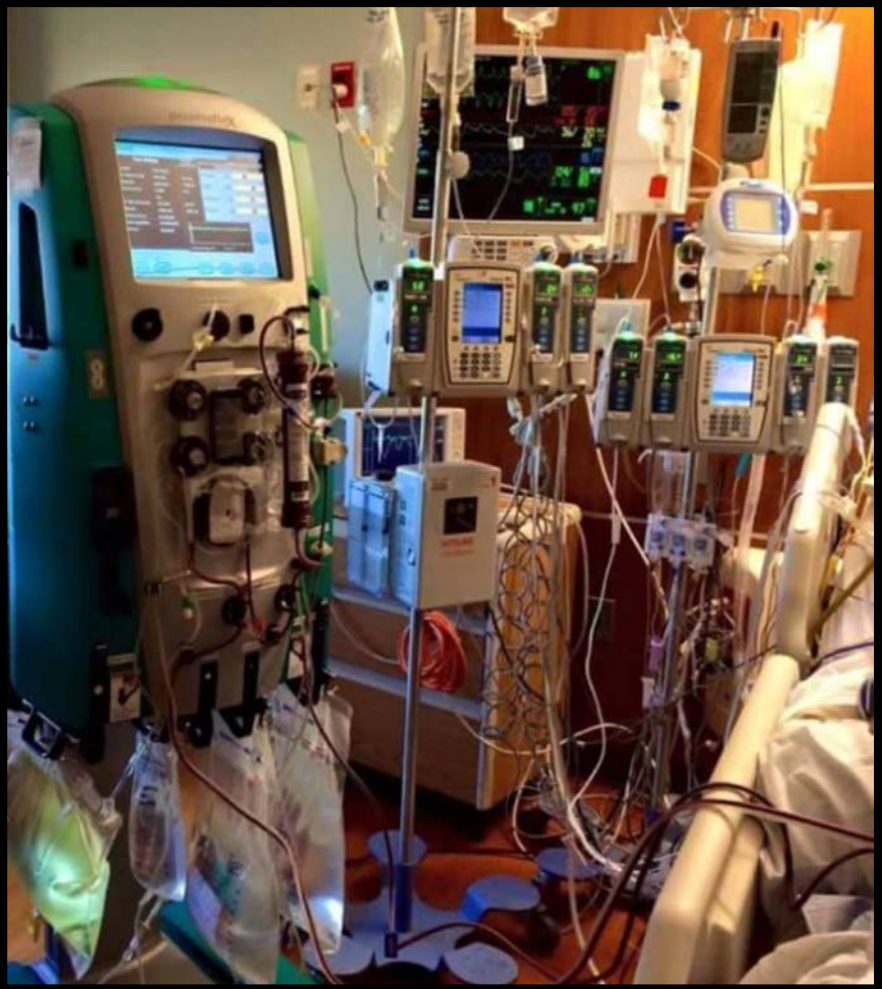
Overview

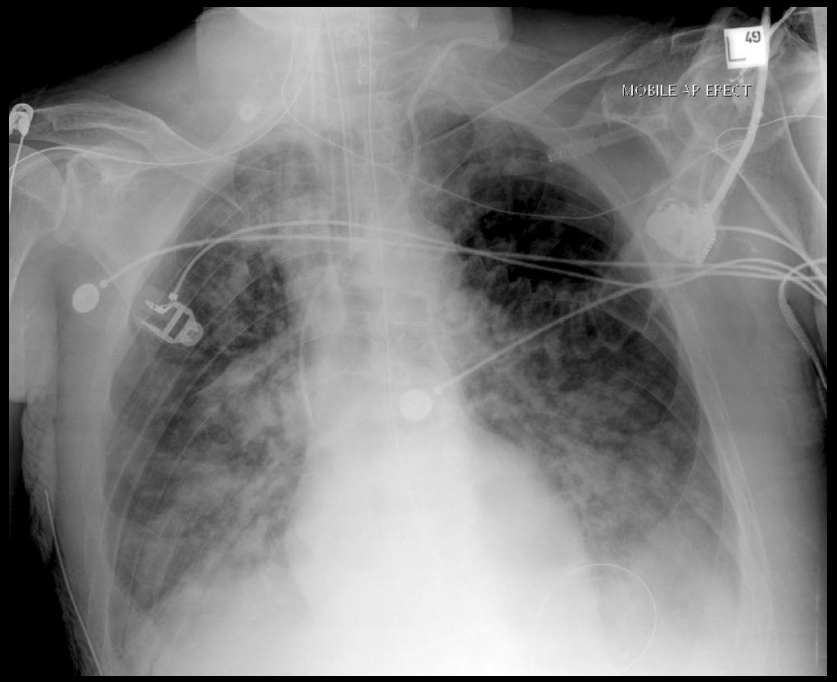
- Diagnosis
- Risk factors
- Therapy
- New developments

A young woman is admitted to the ICU with altered mental status, fever, oliguria, and respiratory distress

- She had undergone an allogeneic stem cell transplant 3 months prior for refractory large B-cell lymphoma
- Had recurrent disease requiring further chemotherapy
- Febrile, neutropenic (total leukocyte count < 500 / microL, low urine production (oliguria < 20 ml/hour)
- Treated empirically with broad-spectrum antibiotics
- Transferred to the ICU

The Intensive Care Environment: Cardiopulmonary monitoring, fluid, vasopressor infusions, sedation, mechanical ventilation, and dialysis





https://www.pinterest.com/pin/53269208070701916
http://www.masimo.com/solutions/perioperative/icu/
Case courtesy of A.Prof Frank Gaillard, Radiopaedia.org, rID: 35985

A young woman admitted to ICU with altered mental status, fever, oliguria, and respiratory distress

- **Severe respiratory failure (hypoxemic)**
  - Mechanical ventilation
- **Low blood pressure (hypotension - shock)**
  - Increasing doses of vasopressors and IV fluids
- **Depressed cardiac function**
  - Biventricular decreased contractility
- **Bleeding disorder**
  - Disseminated intravascular coagulation
- Blood cultures growing a bacterium *Enterococcus faecium*
- **Kidney failure** requiring dialysis
- Next 48 hours - persistent shock, increasing cardiovascular and respiratory support, cardiac arrest and death

A young woman admitted to ICU with altered mental status, fever, oliguria, and respiratory distress

- This patient had an immunosuppressive primary disease treated with stem cell transplantation
- Intensive chemotherapy worsened her immune deficiency and induced a cardiomyopathy
- She developed a blood stream infection (bacteremia) while neutropenic
- Despite prompt broad-spectrum antibiotics and supportive care, she developed:
  - Hemodynamic collapse
  - Respiratory failure
  - Renal failure
  - Microangiopathy
  - Death within a few days

What is Sepsis and Septic Shock?

Clinical Syndromes of Sepsis and Septic Shock

- **Sepsis** is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs
- **Septic shock** is a subset of sepsis in which underlying circulatory, cellular and metabolic abnormalities are profound and substantially increase mortality

JAMA 2016; 315:801

Clinical Syndromes of Sepsis and Septic Shock

Syndromes shaped by:

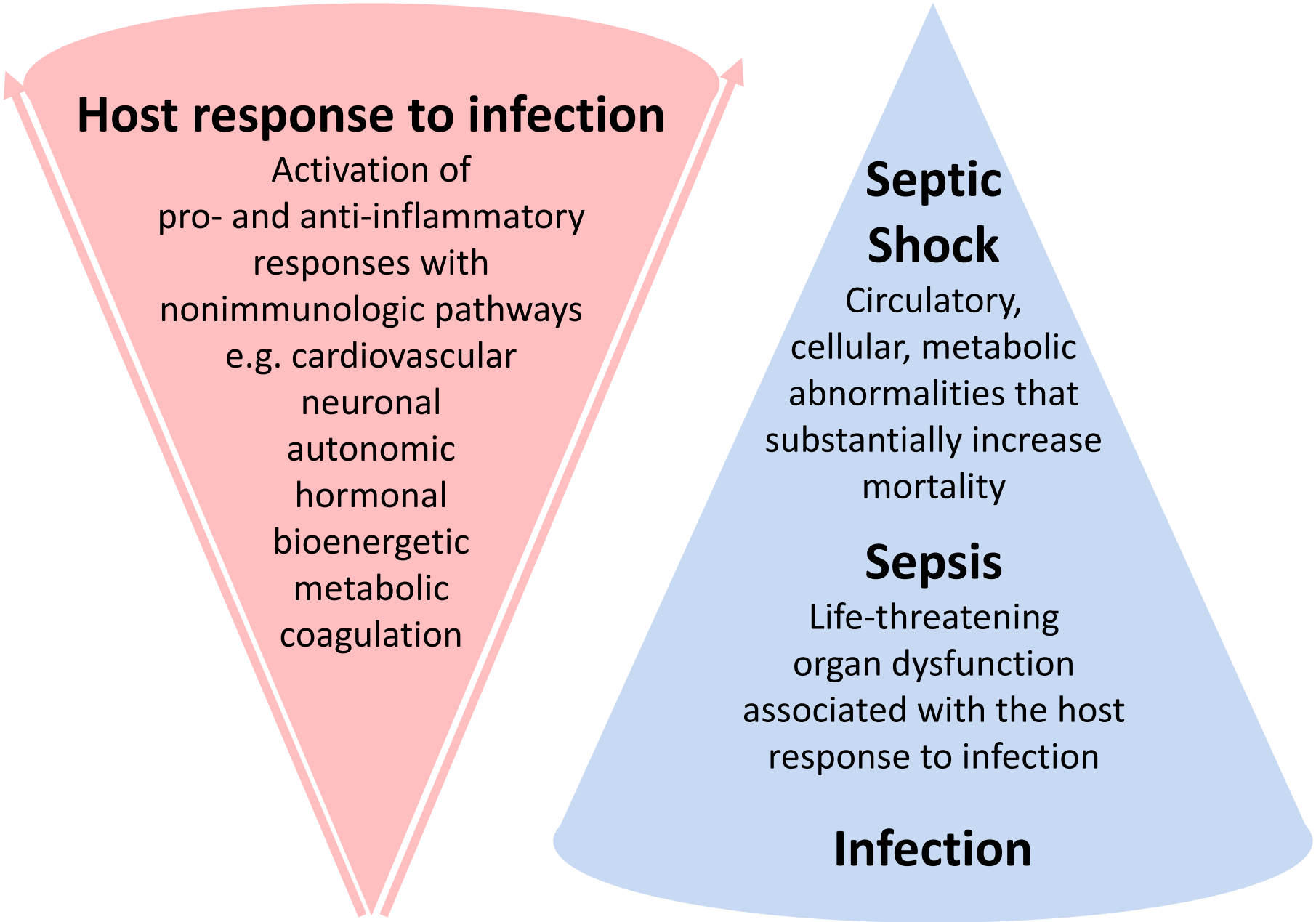
- **Microbial factors**
  - pathogen virulence, etiology, antibiotic resistance
- **Host factors**
  - age, sex, genetics, comorbidities, underlying disease, medications, source of infection
- Characteristics evolve over time
- Biological and clinical heterogeneity

What is the difference between infection and sepsis?

- A consensus definition - sepsis differs from infection by
  - a “dysregulated” host response to infection (impaired physiological regulatory mechanisms)
  - with vital organ dysfunction
- However, no current clinical measures reflect the concept of a “dysregulated” host response
- Organ dysfunction, even when severe, is not associated with substantial cell death

JAMA 2016; 315:801

Sepsis, Septic Shock and the Host Response to Infection




Sepsis
Beauty is in the eye of the beholder

Manifestations of the Clinical Syndromes Called Sepsis and Septic Shock

The presence or the suspicion of an infection and

Systemic Signs	Organ Dysfunction	
Tachycardia	Hypotension	Metabolic acidosis, lactate
Tachypnea	Altered mental status	Respiratory alkalosis
Leukocytosis or leukopenia	Oliguria	Acute lung injury
Fever or hypothermia	Hyperbilirubinemia	Petechiae, cellulitis Pallor, ecthyma gangrenosum
	Coagulopathy	

Manifestations of the Clinical Syndromes Called Sepsis and Septic Shock

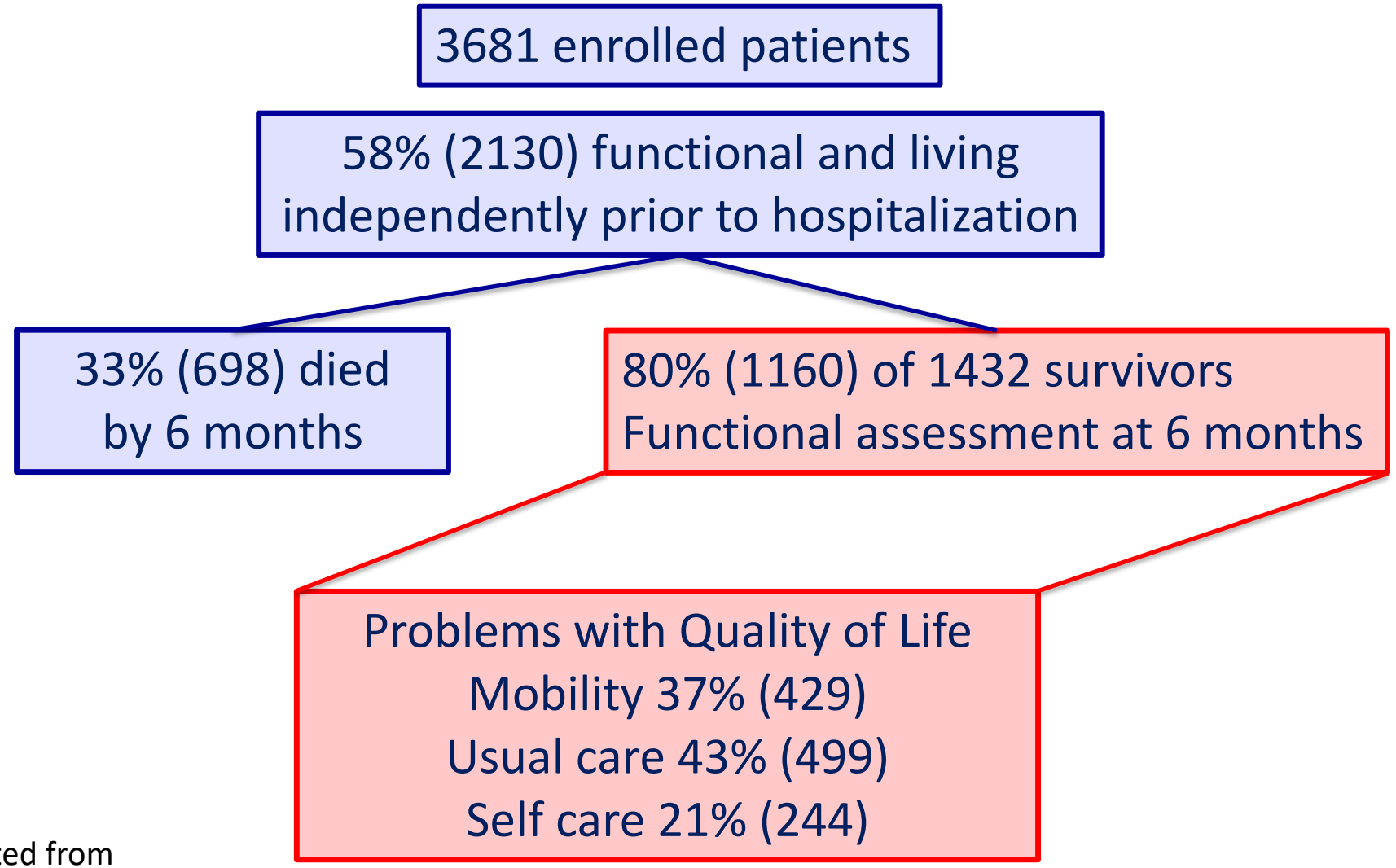
The presence or the suspicion of an infection

and

- No true “gold standard” for diagnosis
- Requires clinical judgement to determine if an infection is present and how the infection is related to alterations in organ function

Fever or hypothermia

Long Term Quality of Life Among Survivors of Severe Sepsis



Adapted from
Crit Care Med 2016;44:1461

Risk of Infection

Neutropenia
Targeted and Biological Therapies

Examples of Increased Susceptibility to Serious Infections from Altered Host Immunity

- Previously healthy
  - Traumatic injury
- Congenital host immune defect
  - Chronic granulomatous disease
- Acquired immune defect
  - Diabetes, alcoholism, smoking
- Acquired diseases
  - Hematologic malignancies
  - HIV
- Immunosuppressive therapies
  - Cancer
  - Immunologic diseases

Neutropenia and Infection Risk

- Patients given cytotoxic therapies may develop a decrease in neutrophil counts
  - < 500 neutrophils / microL
  - variable duration (days – weeks)
  - solid tumors, hematologic malignancies
  - conditioning regimens for stem cell transplants or cell-based immunotherapies
- Lack of normal leukocyte function predisposes to usual and opportunistic infections

Neutropenia and Infection Risk

- Infectious source identified in 20-30% of febrile neutropenia
  - Gram positive bacteria
    - S. epidermidis, S. aureus, streptococci
  - Gram negative bacteria
    - *P. aeruginosa*
- Fungal pathogens more common with prolonged neutropenia
  - *Candida, Aspergillus spp*., *Fusarium spp., Mucormycosis*

Clin Infect Dis 2011; 52:e56

Infection Risks Due to Agents that Target Host Immunity

Target	Example	Risk (+ - +++)
Inhibition of Cytokines or Complement		

Clin Microbiol Infect 2018; 24: S21,S41, S53, S71, S95

Infection Risks Due to Agents that Target Host Immunity

Target	Example	Risk (+ - +++)
TNF	Infliximab, Entanercept	+++ bacteria, viral, fungal Reactivation TB, Histo, Coccidio, Hepatitis B
Complement 5	Eculizumab	+++ encapsulated bacteria (Neisseria spp)

Inhibition of Intracellular Pathways, Tyrosine Kinases
Cell Surface Receptors

Clin Microbiol Infect 2018; 24: S21,S41, S53, S71, S95

Infection Risks Due to Agents that Target Host Immunity

Target	Example	Risk (+ - +++)
TNF	Infliximab, Entanercept	+++ bacteria, viral, fungal TB, Histo, Coccidio, HeBV reactivation
Complement 5	Eculizumab	+++ encapsulated bacteria (Neisseria spp)
Janus kinase	Tofacitinib	+++ risk of infection
Bruton tyrosine kinase	Ibrutinib	++, additive to disease defects and neutropenia, pneumonia, Pneumocystis, invasive fungal, multifocal leukoencephal
VEGF-A/B	Bevacizumab	+++ neutropenia, GI perforation

Inhibition of Lymphoid Cell Surface Receptors

Clin Microbiol Infect 2018; 24: S21,S41, S53, S71, S95

Infection Risks Due to Agents that Target Host Immunity

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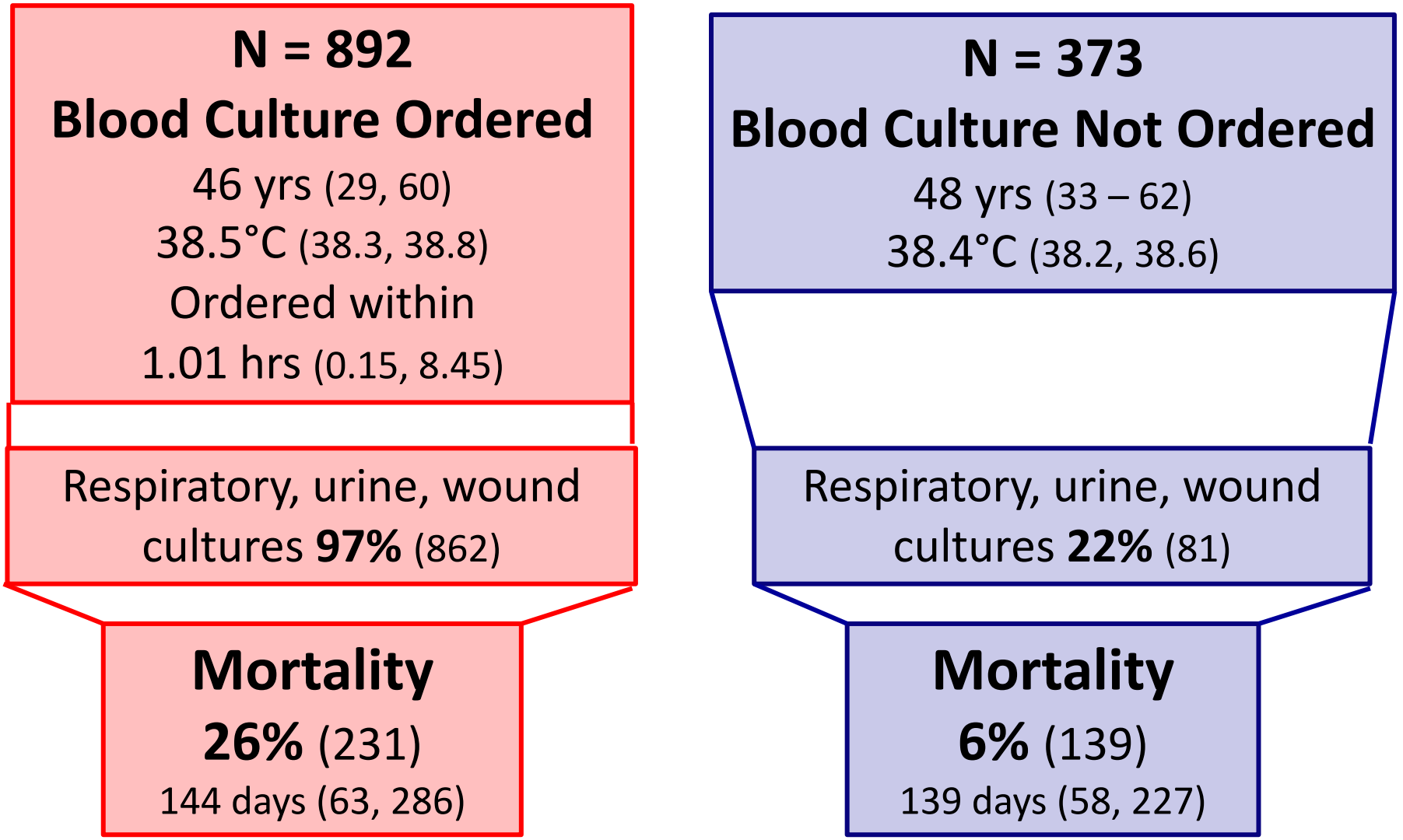
VEGF-A/B	Bevacizumab	+++ neutropenia, GI perforation
CD-20	Rituximab	+++ severe respiratory infections, Varicella zoster, hepatitis B reactivation
CD-52	Alemtuzumab	+++ T cell defect, Pneumocystis, Cytomegalovirus, Herpes simplex virus Reactivitation of hepatitis B and C

Clin Microbiol Infect 2018; 24: S21,S41, S53, S71, S95

1265 NIH Clinical Center In-Patients with 1st Episode of Temperature > 38.1°C



Data from BTRIS, 4/2015-4/2017 median (IQR)

What are the basic elements in caring for an immunocompromised patient in shock?

Young woman with
altered mental status, fever, low urine output,
low blood pressure and respiratory distress

Clinical Assessment and Differential Diagnosis of Shock and Organ Failure

- Differential diagnosis is based on risk assessment
  - What immune defects are present that predispose to infection?
  - neutropenia, previous infections, colonization with resistant pathogens
- Non-infectious conditions can mimic this presentation
  - 2°effect of a cellular therapy, drug reactions, cardiac and pulmonary disorders, acute blood loss from gastrointestinal tract

Diagnostic Approach

Physical exam

- Cardiac, pulmonary, abdominal, neurolgic, skin

Diagnostic tests

- Blood tests: hematology, hepatic, renal, mineral panels, arterial blood gas
- Cultures of blood, respiratory secretions, urine, stains of respiratory secretions, urine, nasal wash for viral and bacterial pathogens, aspiration of skin lesions

Imaging

- Bedside ultrasound exam, CT scan (sinuses, lung, abdomen)

Basics of Therapy

- **Rapid initiation of directed and supportive therapy**
  - Antimicrobial therapy: broad empiric vs directed antimicrobials
  - Intravenous and arterial catheter placement
  - Treat shock with intravenous fluids and vasopressors to restore blood pressure
  - Respiratory support – supplemental oxygen and / or mechanical ventilation

Sites of Infection in Septic Shock

Site of infection	ADRENAL March 2018 % (n = 3713)	APROCCHSS March 2018 % (n = 1241)
Pulmonary	35.0	59.4
Abdominal	25.5	11.5
Urinary	7.5	17.7
Skin / soft tissue	6.8	4.2
1° blood /septicemia	17.3	14
Positive Blood Cultures	34.8	36.6
Documented pathogens	Not specified	71.8

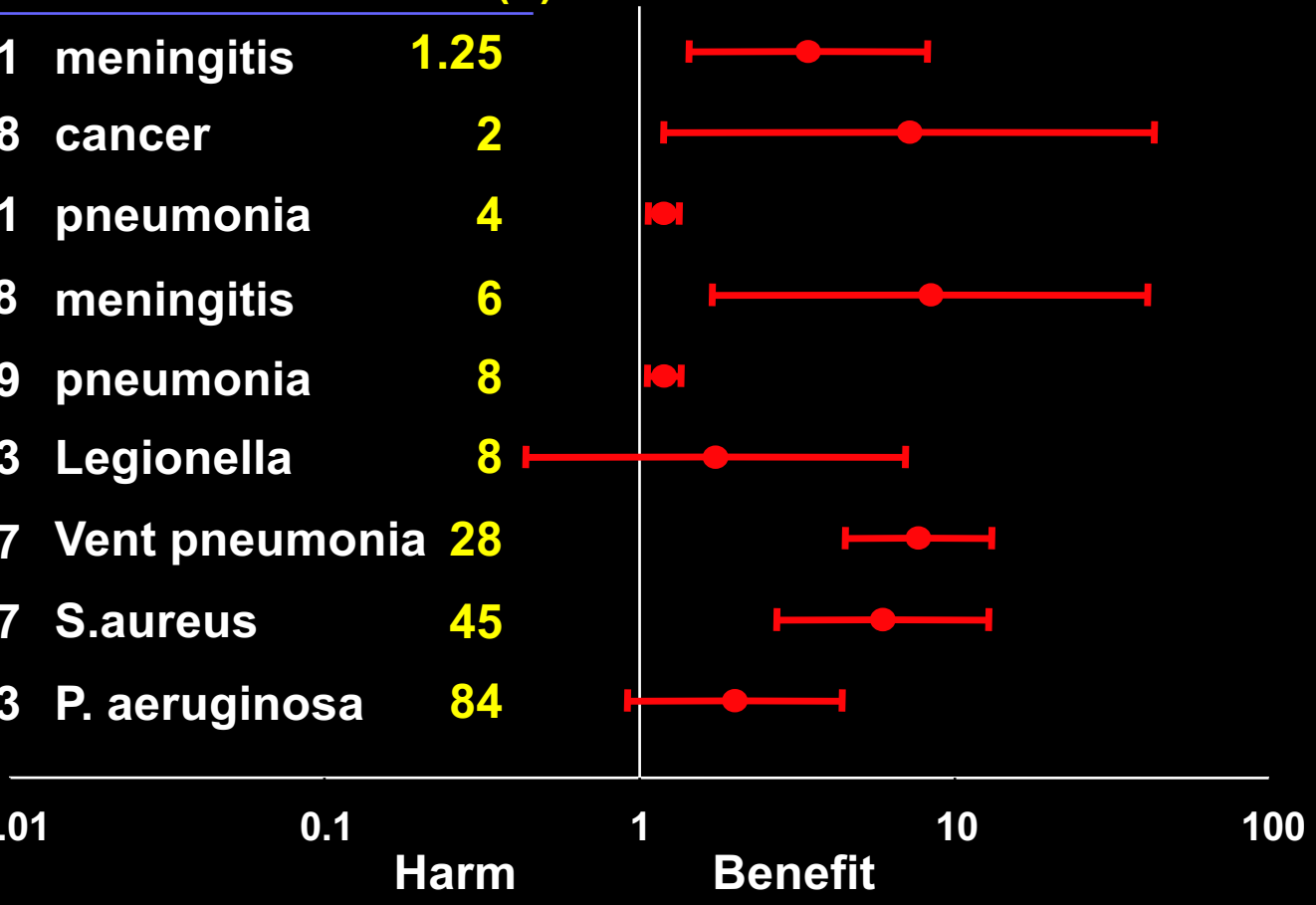
N Engl J Med 2018; 378: 797
N Engl J Med 2018; 3787: 809

Key Elements in the Treatment of Severe Sepsis and Septic Shock

- Early recognition
- Prompt administration of antibiotics
- Titration of intravenous fluids and vasopressors
- If present, remove a nidus of infection

Early vs Late Antibiotics

Author Yr	No.	Diagnosis	< vs > Time (h)
Miner 2001	171	meningitis	1.25
Larche 2002	88	cancer	2
Houck 2004	13,771	pneumonia	4
Proulx 2005	118	meningitis	6
Meehan 1997	14,069	pneumonia	8
Gacouin 2002	213	Legionella	8
Iregui 2006	107	Vent pneumonia	28
Lodise 2003	167	S.aureus	45
Kang 2003	123	P. aeruginosa	84



Odds Ratio of Survival (95% CI)

Time to Initiation of Empiric Antibiotics

The requirement for clinical judgement

Suspected sepsis

Sepsis

Medical urgency

Suspected septic shock

Septic shock

Medical Emergency

Getting back to our patient with septic shock

- Rapid delivery of broad antimicrobial therapy (empiric) e.g. within 1 hour of the order
  - Gram-positive and / or Gram-negative bacteria with attention to prior infections, antibiotic therapy, colonization with resistant organisms
  - If prolonged neutropenia, anti-fungal therapy
- Therapy reevaluated after 1 – 3 days following results of diagnostic microbiology
- Remove potential sources of infection
  - Central venous catheters
  - Collections of fluid around lungs, in abdominal compartment

Themes that Underlie the Resuscitation of Patients in Septic Shock

- Sepsis and septic shock are associated with
  - decreased mitochondrial oxygen consumption
  - decreased ATP production
  - despite normal or supranormal oxygen delivery by enhanced cardiac output
- Altered mitochondrial function may be an adaptive mechanism similar to hibernation allowing stressed cells to recover function

Arch Intern Med 1977; 137:905, JAMA 1993; 270:1724,
N Engl J Med 1994; 330:1717, N Engl J Med 1995; 333:1025
Acta Anaesthesiol Scand 1997; 41(S100): 87
Eur J Clin Invest 2013; 43: 532
Crit Care Med 2013; 41:1774
Shock 2016; 45:271

What tells us the patient is improving?

- Decrease in fever, heart rate, respiratory rate
- Decrease respiratory support
- Stability of blood pressure with decrease in requirement for IV fluids and vasopressors
- Improved sensorium
- Urine output

Will ‘Omics Improve the Diagnosis of Sepsis?

Identify **Pathogens**

Identify **Host Responses** to Infection

Non-culture based methods to identify microbial pathogens

Nucleic Acid Amplification

Targeted (narrow or broad spectrum)

Agnostic (metagenomic)

Direct Molecular Diagnosis of Pathogens from Blood with Nucleic Acid Amplification

Advantages

- Direct detection of pathogen DNA by PCR using selective amplification of specific regions
- High sensitivity and specificity
- Detection of fastidious or non-culturable organisms
- Resistance traits

Direct Molecular Diagnosis of Pathogens from Blood by Nucleic Acid Amplification

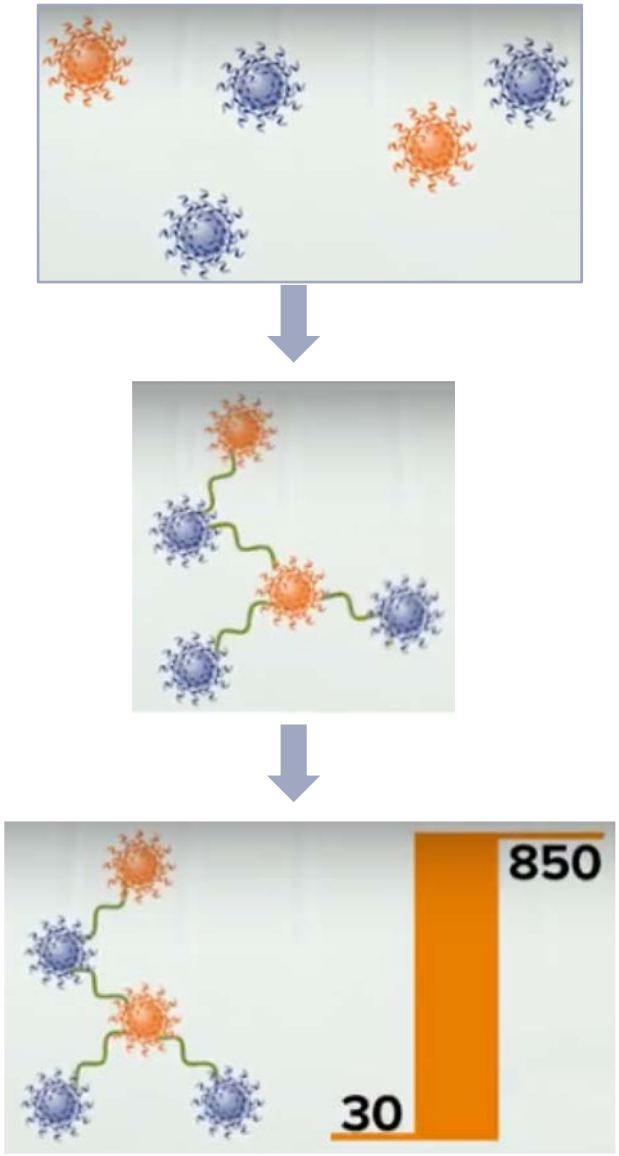
Limitations

- Interference of microbial primers by
  - human DNA, blood components (e.g. iron, immunoglobulins, heparin)
- Limits of detection
- Sensitive to contamination (false positives)
- Amplification of DNA from non-viable organisms
- Resistance
  - Single genes fail to identify multifactorial mechanisms
  - Antibiotic sensitivity requires culture

T2 Magnetic Resonance (T2MR®)

- Targets DNA of pathogen cells directly in whole blood
- Lyse cells, amplify DNA
- Superparamagnetic particles, coated with target-specific binding agents, bind the amplicons inducing aggregation

- Clustering changes the environment of water molecules, alters the magnetic resonance signal (T2 relaxation signal), indicating the presence or absence of the target



https://www.t2biosystems.com/t2mr-technology/

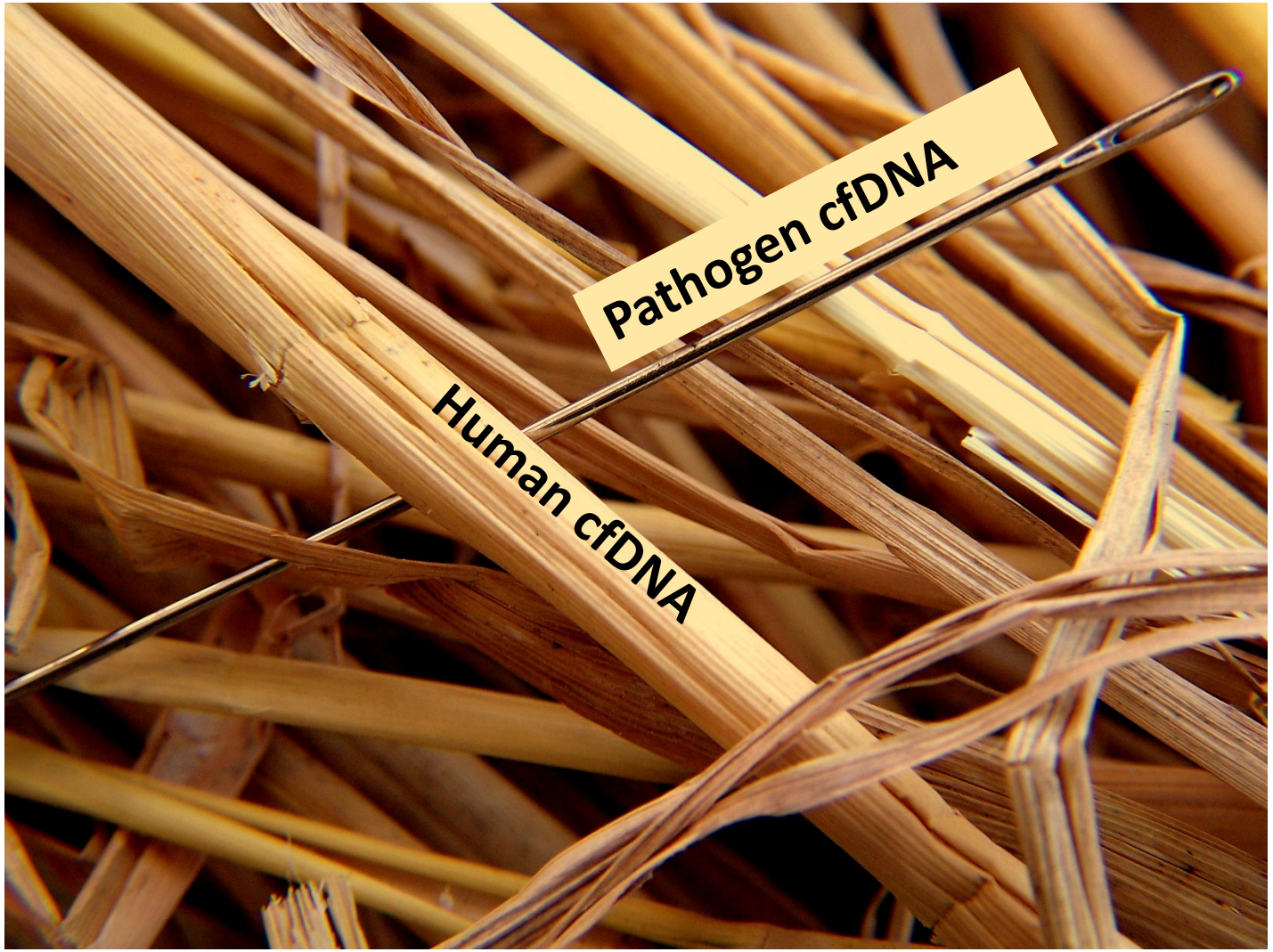
T2 Magnetic Resonance (T2MR®)

Candida Panel (LOD 1 - 3 CFU/ml)	Bacteria Panel (LOD CFU/ml)
C. albicans	*Escherichia coli (8)*
C. tropicalis	*Klebsiella pneumoniae (6)*
C. glabrata	*Pseudomonas aeruginosa (1)*
C. krusei	*Acinetobacter baumannii (2)*
C. parapsilosis	*Staphylococcus aureus (3)*
	Enterococcus faecium (3)

- T2MR will detect intact pathogen cells (viable and non-viable) while on anti-microbial therapy
- Diagnostic sensitivity will depend on pre-test likelihood of presence of infection

Clin Infect Dis 2018 Feb 9, J Clin Microbiol 2018 Feb 14
https://www.t2biosystems.com/t2sepsis-solution/t2bacteria-panel/overview-t2bacteria-panel/

Next Generation Sequencing of Cell-Free DNA (cfDNA) for Pathogen Detection



Harbus.org

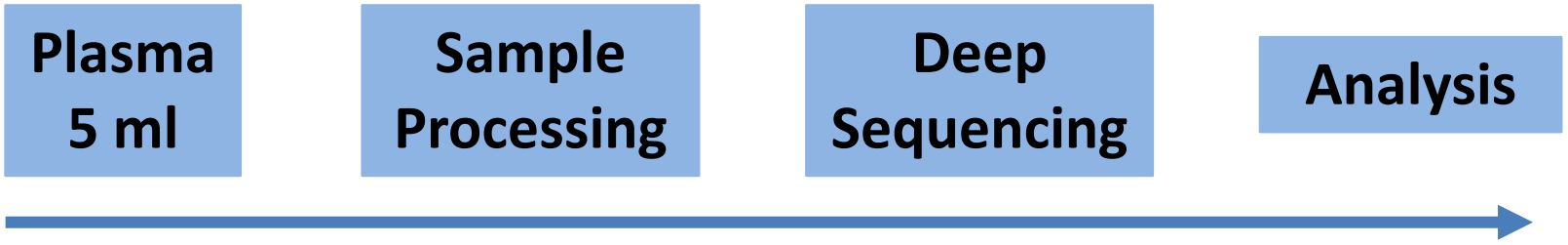
Circulating Cell-Free DNA in Critical Illness

- **Human circulating cell-free DNA**
  - a product of cell necrosis, apoptosis (e.g. trauma, severe sepsis) and active secretion from tumors (liquid biopsy)
- **Human circulating cell-free donor DNA**
  - acute rejection in solid organ transplant
- **Non-human cell-free DNA**
  - as a hypothesis-free approach to test for infection

Sci Transl Med. 2014;6:241ra77
Proc Natl Acad Sci U S A. 2015;112:13336
Genes Chromosomes Cancer. 2018;57:123

Next-Generation Sequencing for Microbial Cell-free DNA

- Proprietary molecular biology and data analysis that uses deep sequencing to detect microbial DNA directly from cell-free DNA in blood (CLIA/CAP Lab)
- Next-generation sequencing to detect fragments of cell-free DNA from **1,250 bacteria, viruses, fungi and protozoa** that may be circulating in bloodstream



Open Forum Infect Dis. 2016 Jul 12;3(3):ofw144
https://www.kariusdx.com

Application of Next-Generation Sequencing (NGS) of Microbial Cell-free DNA in Critical Illness

- 75 septic patients (50 positive blood stream infection (BSI), 25 negative)
  - 80% agreement of NGS with BSI (40/50), 84% negative (21/25)
  - NGS pathogen detection remains positive for longer than blood culture (6 vs 2.4 days)
- Liquid biopsy with NGS identified / confirmed 6 of 9 invasive fungal diagnosis (*Aspergillus terreus, Aspergillus lentulus, Rhizopus sp, Cunninghamella bertholletiae, Scedosporium apiospermum*) 1 – 20 days after biopsies

Wanda L et al. ID Week, San Diego, Oct 7, 2017 Poster #2083
Diagnostic Microbiol Infect Dis 2018; (in press)

Applying Next Generational Sequencing to Critical Illness

- Unbiased, culture independent
- Screen for multiple antibiotic resistance genes
- Control for environmental contamination
- Turn-around time
- Bioinformatics
  - public and curated - proprietary databases

Identifying the Host Response to Infection

Can the expression of the patient's RNA (transcriptomics) help to distinguish the presence of infection from non-infection?

Gene Expression Profiles and Critical Illness Syndromes

- Many critical illnesses are syndromes that arise from multiple causes and underlying conditions
- If the entire spectrum of a syndrome has a common molecular pathophysiology, then a molecular biomarker(s) should exist

Crit Care Med 2017; 45:934

Gene Expression Profiles and Critical Illness Syndromes

- Transcriptomic data from RNA microarrays are analyzed across multiple cohorts
  - Increases power
  - Biologic and technical heterogeneity
  - Imperfect comparisons
    - Studies may have different criteria for a disorder (respiratory distress, sepsis)
- Thousands of potential biomarkers can be examined
  - False positive associations more likely when more variables than samples in a study

Crit Care Med 2017; 45:934

Can gene expression profiles serve as biomarkers for sepsis?

Comparison	Performance	Results
Sepsis (n = 327) vs **sterile inflammation** (n= 326) 27 data sets	AUC 0.87; range 0.7 – 0.98	*CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, HLA-DPB1 (*Sepsis MetaScore genes)
Bacterial vs **viral infection** (adults, children) 767 samples 30 cohorts	antibiotic decision model sensitivity (94%) and specificity (59.8%) for bacterial infection	*IFI27, JUP, LAX1, HK3, TNIP1, GPAA1, CTSB with previous* Sepsis MetaScore genes

Sci Transl Med 2015; 7: 287ra71
Sci Transl Med 2016; 8: 346ra91

Can gene expression profiles serve as biomarkers for sepsis?

Comparison	Performance	Results
Bacterial infection in febrile infants < 60 days old n = 80 bacterial 190 without bacterial infection 19 afebrile healthy	94% sensitivity 95% specificity	*BATF, MSRA, ALOX5AP, PADI4, RAB27A, FCAR, MGAM, HNRNPA3P1, MMP9, HSH2D*

JAMA 2016; 316:846

Can gene expression profiles serve as biomarkers for sepsis?

Comparison	Performance	Results
Adults with acute respiratory illness Derivation cohort: 115 viral 70 bacterial, 88 noninfectious, 44 healthy Validation cohort: N = 328	Accuracy 87% AUC 0.90 – 0.99	134 genes identified using microarray to identify causes of sepsis 74 bacterial 26 viral 29 noninfectious

Sci Transl Med 2016; 8: 322ra11

Molecular Host Response Assay to Discriminate Sepsis from Noninfectious Systemic Inflammation

- Relative expression of 4 genes *CEACAM4, LAMP1, PLAC8, PLA2G7* (SeptiCyte LAB) in 447 patients
- Estimated AUC 82 – 89% for discriminating sepsis from noninfectious systemic inflammation

Retrospective Diagnosis	Sepsis	Systemic Inflammation	Indeterminate
Unanimous 3 of 3 agree	27% (119)	38% (171)	-
Consensus 2 of 3 agree	40% (180)	51% (240)	8% (37)
Forced All disagree, 2nd review	45% (202)	55% (245)	-

Am J Respir Crit Care Med 2018; 198:903

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Considering the heterogeneity among:

- Underlying conditions
- Microbial pathogens
- Host immunity

the application of transcriptomic tests will require extensive validation before they can be used clinically

Am J Respir Crit Care Med 2018; 198:903

Will Big Data from Transcriptomics, Proteomics, Metabolomics Improve the Diagnosis of Sepsis in Critically Ill Patients?

- Probably, but….
- Cost
- Bioinformatics
- Work flow
- Integration of microbial, host transcriptomics proteomics, metabolomics will be challenging
- Will these technologies affect outcome?

Inflammatory Syndromes and Critically Ill Patients

Syndromes of “inflammation” without a detectable pathogen may be related to:

- Fragments and remnants of known pathogens
- Non-culturable pathogens
- Previously unrecognized / novel pathogens

Thank you